I. WITHDRAWN REJECTIONS

The Examiner has withdrawn the rejection of pending claims 1-3 under 35 U.S.C. § 102 as allegedly being anticipated by Rink *et al.* (US 5,739,106) (November 13, 2000 Office Action, ¶ 7).

The Examiner has also withdrawn the rejection of pending claims 4-6 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rink *et al.* (US 5,739,106) in view of Gaeta *et al.* (US 5,686,411) (November 13, 2000 Office Action, ¶ 8).

Additionally, the Examiner has withdrawn the rejection of pending claims 1-6 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kolterman *et al.* (*Diabetologia* 39:492-99 (1996)) ("Kolterman I") or Kolterman *et al.* (WO 96/40220) ("Kolterman II") or Moyses *et al.* (*Diabetic Med.* 13:34-38 (1996)) or Thompson *et al.* (*Diabetes* 46:632-36 (1997)) in view of Cooper *et al.* (*Biochim. Biophys. Acta* 1014(3): 247-58, abstract (1989)) and Rink *et al.* (US 5,739,106) (November 13, 2000 Office Action, ¶ 9).

II. NEW REJECTIONS

Double Patenting Rejection

The Examiner has provisionally rejected certain pending claims under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over the claims of co-pending application SN 09/445,517 (November 13, 2000 Office Action, ¶ 10). The Examiner has stated that although the pending claims are not identical to those in co-pending application SN 09/445,517, the claims are not patentably distinct from each other because of the overlapping scope of the claims.

The Examiner's rejection is unclear as to which, or all, of the pending claims have been rejected on these grounds. Applicants respectfully request the Examiner to clarify the rejection by identifying which pending claims have been provisionally rejected for alleged double patenting. In light of the provisional nature of this rejection, Applicants further request that the Examiner hold this matter in abeyance until receipt of official notification of allowable claims in this and/or co-pending application SN 09/445,517.

35 U.S.C. § 103(a) [Claims 1-3] - Rink *et al.* ('106)

The Examiner has rejected claims 1-3 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rink *et al.* (US 5,739,106) (November 13, 2000 Office Action, ¶ 11). Rink *et al.* is assigned to Amylin Pharmaceuticals, owner of the instant application, and is directed to compositions and methods for reducing food intake, suppressing appetite and controlling body weight. The claimed compositions include compositions containing both an amylin agonist and a CCK agonist, or hybrid peptides incorporating features of amylin agonist peptides and CCK agonist peptides.

The Examiner acknowledges at page 4 of the Office action that Rink *et al.* ('106) "differ [sic] from the instant invention in not using their method for treating 'obesity' in a human." The Examiner is also apparently aware that the Rink *et al.* patent is directed to amylin agonist–CCK agonist combinations and methods of administration, as well as hybrid amylin agonist-CCK agonist peptides. The Examiner alleges, however, that Figure 1 of the Rink '106 patent illustrates that administration of amylin alone suppressed food intake in mice, and asserts that "Figure 1 depicts that amylin alone, when injected at 2 microgram/kg, induced more than 50% inhibition in food intake." The Examiner concludes from this assertion that it would have been *prima facie* obvious for one of skill in the art at the time the invention was made "to use or extend" the method of suppressing food intake in Rink *et al.* ('106) "to produce the method of instant invention" with a "reasonable expectation of success."

Applicants respectfully traverse the rejection, and submit that the Examiner has not established a *prima facie* case of obviousness. The Examiner argues that it would have been obvious to one of skill in the art to develop the methods of treating obesity in humans from the appetite suppression in mice allegedly described in the cited document. Rink *et al.* ('106), however, does not teach any method of treating the complex disease of obesity, which involves many factors, only one of which is food quantity intake (i.e., caloric intake discussed in the present application), nor does it describe or suggest the specific methods of treating obesity claimed by applicants.

Rink *et al.* ('106) is directed to (1) a composition that includes an amylin agonist admixed with a cholecystokinin ("CCK") agonist, (2) a composition that includes a hybrid

peptide that incorporates features of both amylin agonist peptides and CCK agonist peptides, and (3) co-administration of an amylin agonist and CCK agonist. Thus, Rink *et al.* ('106) does not teach, describe or suggest the use of an amylin agonist alone for controlling appetite in mice, let alone for treating obesity in human subjects. Rink *et al.*, furthermore, plainly teaches away from the use of the instant claimed invention regarding the use of amylin agonists, as it instructs the need for, and commands the use of, amylin agonist–CCK agonist combinations, combined administration of amylin and CCK agonists, or related hybrid peptides incorporating the features of both peptides.

The Examiner contends that, in column 14, Rink *et al.* ('106) explicitly teaches, by referencing Figure 1, that rat amylin "alone" suppressed food intake. But Rink *et al.* ('106) explains that this result is "not significant" at column 22, lines 31-33. Specifically, the Rink '106 patent states (at column 22, lines 28-37) that injection of amylin at a dose of 1.0 microgram/kg had no effect on food intake:

> As shown in FIG. 1, rat amylin (AC128) (1.0 μg/kg) and CCK-8 (1.0 μg/kg) alone and in combination suppressed food intake in mice at 30 minutes. Rat amylin plus CCK-8 suppressed food intake by 72.3.+-.7.5% (P<0.0006). Rat amylin alone suppressed food intake by -10.5.+-.10.3% (not significant). CCK-8 alone suppressed food intake by 10.6.+-.16.9% (not significant). The dose response for appetite suppression in mice of rat amylin (AC128) (filled circles), CCK8 (open circles) and rat amylin plus CCK (filled squares) is also shown in FIG. 1 [emphasis added].

The words "alone and" in line 2 of the above-quoted paragraph can only represent a typographical error to the extent that one were to suggest them to mean that amylin alone at 1.0 microgram/kg had an effect on food intake, for the data in Figure 1 and the data referenced in the body of the patent (quoted above) plainly show otherwise. Indeed, the statement at column 22, lines 31-33, indicating that the experimental results showed that "amylin alone suppressed food intake by -10.5.+-.10.3% (not significant)" actually represents—give the negative value of the number—a stimulation of food intake at a dose of 1.0 microgram/kg.

Thus, in light of this teaching in Rink *et al.* ('106), one of ordinary skill in the art would not have found it obvious to use amylin or an amylin agonist to treat a specific and complex disease (obesity) in a different species (humans). This is particularly so in light of the fact that effective anti-obesity dosages shown in Example 1 of the instant application include a 60 microgram dose which – given the 70 kilogram average weight of a human – equals a dose that is less than the 1.0 microgram/kg dose shown in the Rink '106 patent to have no effect (or a stimulatory effect) on food intake.

Applicants also wish to point out that the Examiner has mistaken the X coordinate "2" in Figure 1 of the Rink '106 patent. In the November 13, 2000 Office Action at page 4 the Examiner concluded that,

> Figure 1 depicts that amylin alone, when injected at 2 microgram/kg, induced more than 50% inhibition in food intake at 30 minutes [emphasis added].

However, Applicants note that the X axis in Figure 1 of the Rink '106 patent is drawn on a log scale. The coordinate "2" thus refers to "100 microgram/kg" rather than "2 microgram/kg." Similarly, Applicants further note that the X coordinate "1" refers to 10 microgram/kg, the "0" coordinate refers to 1.0 microgram/kg, the "-1" coordinate refers to 0.1 microgram/kg (or 100 nanogram/kg), the "-2" X-axis coordinate refers to 0.01 microgram/kg (or 10 nanogram/kg). This is important because, referring to Figure 1 of the Rink '106 patent and the point on the curve just to the right of the "0" coordinate (which is equal to 1.0 microgram/kg), it is equally clear that the injection of amylin alone at 2.0 microgram/kg would also have no effect on food intake (aside from a potential effect to increase food intake given that the point on the curve is below zero, thus indicating weight gain).

Indeed, the basis for the Rink *et al.* ('106) invention is not the use of amylin or an amylin agonist as an appetite suppressant, let alone a composition for the treatment of obesity. To the contrary, Rink *et al.* ('106) set out the basis for their invention in the Summary of the Invention at column 7, lines 14-23, where they report that injection of 1 μg/kg of amylin had no effect on food intake. Rink *et al.* ('106) states:

> Applicants have discovered that amylin agonists and CCK agonists when administered together have a synergistic effect on reduction of food intake. The present application describes the use of any amylin agonist in conjunction with a CCK agonist for the control of food intake. For example, an IP injection of 1.0 µg/kg CCK-8 or 1.0 µg/kg rat amylin has no measurable effect on food intake. But administration of 0.1 µg/kg of each peptide causes a substantial reduction of food intake about equivalent to that seen with 100 µg/kg of either peptide alone [emphases added].

Thus, the Examiner's cited teaching in Rink *et al.* ('106) actually stands for the proposition that appetite suppression in mice, upon administration of rat amylin, is "not statistically significant." Rink *et al.* ('106) nowhere describes or suggests the use of amylin or amylin agonists alone for the treatment of obesity in humans, and indicates that administration of amylin alone into experimental animals "has no measurable effect on food intake" at 1.0 microgram/kg. Plainly, it would not have been obvious to one of skill in the art at the time the invention was made to arrive at the presently claimed methods of treating obesity in humans with an amylin or an amylin agonist, using Rink *et al.* ('106) which taught the ineffective use of an amylin in suppressing appetite in mice and disclosed no methods of treating obesity.

Because Rink *et al.* ('106) does not show any treatment of obesity, the Examiner has apparently relied on the general knowledge of one of ordinary skill in the art to provide a teaching, motivation or suggestion for methods of treating obesity with a composition comprising an anti-obesity agent consisting of an amylin or an amylin agonist. Such motivation, however, would have been contrary to the teachings in the art at the time the invention was made. To this point, the Examiner has overlooked evidence presented by applicants that before the instant invention amylin and amylin agonists had never before been used or suggested to treat obesity in humans and that studies actually demonstrated the opposite, namely the effective and preferred use of amylin ***antagonists***, *i.e.*, compounds that actually ***block*** the normal effects of amylin, to treat obesity. *See, e.g.*, Amylin Pharmaceuticals' U.S. Patent No. 5,280,014, issued January 18, 1994, and U.S. Patent No. 5,364,841, issued November 15, 1994, both entitled, "Treatment of Obesity and Essential Hypertension and Related Disorders." Both patents are

directed to the treatment of obesity using amylin ***antagonists*** in order to block amylin activity. *See, e.g.,* claim 2 of the '014 Patent; and claim 2 of the '841 Patent. This is in contrast to the presently claimed invention, which uses amylin agonists in one embodiment to enhance such activity.

Also teaching away from the methods of treating obesity described and claimed in the instant application is U.S. Patent No. 5,656,590, issued on August 12, 1997 to Rink *et al.* for "Treatment of Anorexia and Related States." "[I]n general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130, 1131 (Fed. Cir. 1994), citing the United States Supreme Court decision and opinion in *United States v. Adams*, 383 U.S. 39, 52, 148 U.S.P.Q. 479, 484 (1986) ("known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness"). The Rink '590 patent describes and claims methods for the treatment of patients suffering from anorexia or a similar condition by administering an amylin or an amylin analogue in order to increase weight.

Thus, the evidence of record shows, in contrast to the Examiner's conclusion that it would have been obvious to use amylin or an amylin agonist to treat obesity, the art teaches the opposite, and one of skill in the art would not have been motivated to use the available amylin or amylin agonists by themselves for methods of treating obesity. Amylin Pharmaceuticals, which for the last decade has been the world leader in the investigation and development of amylin and amylin agonist molecules for the treatment of human disorders, had itself determined that it was amylin ***antagonists*** rather than amylin ***agonists*** that would find utility in the treatment of obesity and that, in fact, the use of amylin agonists as a treatment for anorexia would lead to weight gain rather than weight decrease. *See* the '841, '014 and '590 patents.

The Examiner has not provided any reason why one of ordinary skill in the art at the time the invention was made would have modified Rink *et al.* to eliminate an explicitly required part of the invention claimed therein – *i.e.*, eliminating CCK from the described amylin agonist–CCK combinations, methods of amylin agonist–CCK agonist administration, or eliminating the CCK function from the related hybrid peptide inventions – in a theoretical attempt to arrive at the

instantly claimed invention. Applicants respectfully submit that the Examiner is impermissibly using hindsight gained from Applicants' present teachings to bridge the gap from the methods of appetite suppression in mice by coadministration of an amylin agonist admixed with a CCK agonist (or a hybrid peptide) to arrive at the presently claimed invention.

Further in this regard, Applicants wish to draw the Examiner's attention to the Manual of Patent Examining Procedure (MPEP) §2144.04. MPEP §2144.04 states that "omission of an element and retention of its function is an indicia of unobviousness." In doing so, reference is made to *In re Edge*, 359 F.2d 896, 149 USPQ 556 (CCPA 1966). Various arguments by Applicants focus on the fact that the Examiner is applying documents directed toward appetite suppression in mice using a combination of components, as the basis for asserting that the presently claimed invention would have been obvious within the meaning of 35 U.S.C. § 103. The Examiner is further equating food intake reduction (i.e., appetite suppression) with obesity treatment, although obesity is not necessarily linked to food intake (*see, e.g.*, the discussion of Arnelo I below)..

Even it were assumed, *arguendo*, that the Examiner's assertions that appetite suppression in mice using an amylin agonist-CCK agonist combination (by method or composition) or hybrid peptides including both functionalities could be proved to establish a *prima facie* case that the treatment of obesity in humans using an anti-obesity agent consisting of an amylin or an amylin agonist is obvious, the MPEP and *In re Edge* are on point. The fact that Applicants' invention is directed toward treatment of obesity in humans using amylin or an amylin agonist, without requiring other components (e.g., CCK agonists or CCK agonist functionality, as required by certain cited documents) is indicia of unobviousness of the presently claimed invention.

For reasons set forth herein, Applicants submit that they have rebutted the Examiner's assertion regarding the existence of a *prima facie* case of obviousness and request that this rejection be reconsidered and withdrawn.

35 U.S.C. § 103(a) [claims 1-4] - Arnelo *et al.* I or Arnelo *et al.* II;)

The Examiner has rejected claims 1-4 under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Arnelo *et al.* , *Am. J. Physiol.* 271:6 pt 2:R1654-R1659 (1996) (Arnelo, *et al.* I) or Arnelo, *et al., Scand J. Gastroenterol.* 31:83-89 (1996) (Arnelo, et al. II) at page five of the November 13, 2000 Office Action. The Examiner states that:

> The method of treatment of obesity is viewed as the same as the reduction in body weight in light of the experimental results presented in Example 1 of the instant specification.

Applicants respectfully traverse this rejection and submit the Examiner has not made out a *prima facie* case of obviousness.

Arnelo *et al.* I reported that the purpose behind the experiments described therein "was to investigate the dose–response effect of long-term administration of IAPP[1] on food intake and meal patterns in rats." Arnelo *et al.* I at R1654, column 2.[2]. Arnelo *et al.* I would not suggest to one of ordinary skill in the art any method of treating obesity, as there was in fact no reported weight loss in the experimental rats during the study. Figure 4 of Arnelo *et al.* I shows the rats consistently gained weight, although there was decreased body *weight gain*. However, all rats

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1 While Arnelo *et al.* I state that IAPP and amylin are the same, applicants note that one of the co-authors of Arnelo *et al.* I, Per Westermark, previously reported and defined IAPP as a different molecule from amylin. Specifically, unlike amylin, IAPP was not defined as a 37 amino acid peptide having a C-terminal amide and disulfide bridge between amino acids at positions at 2 and 7 positions of the peptide. *See* U.S. Patent No. 5,116,948, "Preparations of islet amyloid polypeptide (IAPP) and antibodies to IAPP," issued on May 26, 1992 to Westermark and Johnson. Thus, absent a specific indication that Westermark equates IAPP with the amylin discovery of Garth Cooper and Antony Willis (U.S. Patent No. 5,367,052, "Amylin Peptides") and actually used amylin and not his patented IAPP molecule, one of skill in the art would not necessarily have applied Westermark and Arnelo's teachings relating to IAPP to the amylin art.

2 Arnelo *et al.* I relates to continuous or "chronic" administration of IAPPs, compared to the presently claimed invention, which includes discrete dosages of an amylin or amylin agonist. Arnelo *et al.* I, in fact, at page R1657, column 2 shows to one of skill in the art that "it remains to be determined whether discontinuous modes of IAPP administration would produce less desensitization and marked effects on feeding."

tested gained weight during the study, even at the highest doses of administered IAPP. Positive weight gain would not be considered by one of skill in the art as the method of treating obesity, and thus Arnelo *et al.* I would not be pertinent to one of skill in the art concerning methods of treating obesity and does not teach or suggest presently claimed methods of treating obesity. This is particularly so in light of the admission in Arnelo I, at page R1658, that the alleged "anorexic" dosages of material administered lead to the same plasma levels found in obese rats. According to Arnelo *et al.*,

> Plasma IAPP levels produced by anorexic doses of IAPP in rats in the present study (35 to 240 pM) are within the range of endogenous plasma IAPP levels measured in genetically insulin-resistant obese Listar Albany rats . . . . [emphases added.]

Also unlike applicants' invention, which claims methods of treating the disease of obesity, any effect of chronic IAPP administration in Arnelo *et al.* I was "transient," even over the reported eight day experiment. For example Arnelo *et al.* I state:

> The anorexia produced by 8 days of IAPP administration was transient, with more prolonged effects at higher doses and during the light phase. [Arnelo *et al.* I, at page R1656, column 2, paragraph 4 – R1657 first paragraph; emphasis added].

The transient effects on food intake reported in Arnelo *et al.* I in weight-gaining rats – using doses that produce plasma IAPP levels similar to those of obese rats – would not suggest the presently claimed methods of treating obesity in humans.

Arnelo *et al.* I also report that the mean meal size and the mean meal duration did not change during the course of the study with administration of IAPP, but that the effects in the decrease of weight gain was seen by a decrease in the average number of meals taken. Arnelo *et al.* I, page R1657, bridging paragraph between columns 1 and 2. One of ordinary skill in the art would not view these results as directly applicable to methods for treating obesity in humans. Humans do not take meals as frequently per day as do rats, and any proposed method of treating obesity in humans that only decreased the number of meals taken would not suggest a viable method of treating obesity in humans. It would not have been obvious to those in the art to

transform Arnelo *et al.* I's experiment with IAPP in rats and extend it to the presently claimed methods of treating obesity in humans.

Arnelo *et al.* II is similarly unrelated to Applicants' claimed methods of treating obesity in humans. It also concerns the administration of IAPP in rats. Moreover, Arnelo *et al.* II report that, "Bolus injection or infusion of human IAPP did not inhibit food intake at any dose" and that suppression of feeding on administration of rat IAPP bolus injection and infusion effects had vanished by 24 hours at the 5 and 10 nmol/kg doses. Arnelo *et al.* II, at page 85, last paragraph. If the Arnelo *et al.* II authors mistakenly referred to IAPP as amylin, and converting their nanomole doses to micrograms, these two ineffective dosages are both equivalent to over 1300 μg and 2700 μg doses in a 70 kg adult human. If such high doses were ineffective one of ordinary skill art could not conclude that IAPP, let alone the amylins and amylin agonists claimed in the instant application, would be effective to treat human obesity.

Furthermore, although the chronic (*i.e.* continuous) administrations of IAPP reportedly decreased body weight in the initial portion of the experiment, by the sixth day of continuous infusion, the rats were increasing in body weight. Because of this, and the fact that the rats were increasing in body weight at the end of the study, one of ordinary skill in the art would not be motivated to apply the Arnelo *et al.* II teachings to arrive at applicants' claimed methods of treating obesity in humans. Arnelo *et al.* II caution that "the reduced effect of IAPP with time during long-term exposure should be noted" and this would not motivate one of skill in the art to apply the teachings of Arnelo *et al.* II to any treatment of obesity where sustained weight loss would be important.

In sum, there is no teaching, suggestion or motivation in either the Arnelo *et al.* I or Arnelo *et al.* II documents to arrive at applicants' claimed method of treating obesity in humans. Applicants request that this rejection also be reconsidered and withdrawn.

35 U.S.C. § 103 [Claims 5-6] – Arnelo *et al.* I or II As Applied to Claims 4 and 1, and Further In View of Bennett *et al.*

The Examiner has also rejected claims 5 and 6 for alleged obviousness under 35 U.S.C § 103(a) over Arnelo *et al.* I or Arnelo *et al.* II as applied to pending claims 4 and 1, and further in

view of Bennett *et al.* (U.S. Patent No. 5,955,433, "Method of Thrombin Inhibition") (November 13, 2000 Office Action, ¶ 13). Applicants respectfully traverse this rejection.

Applicants submit that the Examiner has not established a *prima facie* case of obviousness because the Bennett *et al.* "thrombin inhibition" patent does not supply any of the elements of applicants' invention that are missing from the Arnelo *et al.* (I or II) documents. Bennett *et al.* is not pertinent to an evaluation of applicants' claimed invention as it does not concern methods of treating obesity, the administration of an amylin or an amylin agonist, or dosage frequencies or amounts related thereto. Instead, Bennett *et al.* is directed to:

> Compositions and methods for the treatment and diagnosis of diseases or disorders amenable to treatment through modulation of expression of a nucleic acid encoding a platelet endothelial cell adhesion molecule-1 (PECAM-1; also known as CD31 antigen or endoCAM) protein.... [Bennett *et al.*, abstract]

Claim 5 of the present application, dependent from claim 4, specifically claims methods that include administering a composition comprising an amylin or an amylin agonist from 1 to 4 times per day. Claim 6, dependent from claim 5, further claims methods where the amylin or amylin agonist is administered in an amount from 30 μg/dose to 300 μg/dose. None of these claim features is found in Bennett *et al.* as cited by the Examiner, and under the law, this document when combined with either or both Arnelo documents above, is insufficient to support a *prima facie* case of obviousness.

Alleged prior art references or a combination of alleged references must teach or suggest all the limitations of the claims. *See In re Wilson*, 165 USPQ 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art."). Moreover, the teachings or suggestions, as well as the expectation of success, must come from the prior art, not applicants' disclosure. *See In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). There are no teachings, suggestions or expectation of success relating to the administration of an amylin or an amylin agonist in Bennett *et al.*, nor does the document even discuss the disease of obesity. Further, the claimed dose amounts and frequencies are not found in any of the cited documents. At best, the Examiner's rejection amounts to an "obvious to try" rejection, the assertion being that one of the ordinary skill in the art would allegedly be

motivated to experiment with a barrage of different dosage amounts and frequencies to arrive at applicants' invention in claims 5 and 6. This type of rejection has been deemed improper time and time again by the Federal Circuit: "Obvious to try" has long been held not to constitute obviousness. A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." In re *Deuel*, 34 U.S.P.Q.2d 1210, *citing* In re *O'Farrell*, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988). The rejection fails, furthermore, because there is no base document which one might modify to "try" different dosages.

Applicants respectfully request that this rejection also be reconsidered and withdrawn.

35 U.S.C. § 103(a) [claims 1-6] Kolterman *et al.* II in View of Meglasson

The Examiner has rejected claims 1-6 under 35 U.S.C. § 103(a) as allegedly unpatentable over Kolterman *et al.* (WO 96/40220; Kolterman *et al.* II) in view of Meglasson (U.S. Patent No. 5,134,164, "Use of 3-Guanidinopropionic Acid in the Treatment of Excess Adiposity") (November 13, 2000 Office Action, ¶ 14). Applicants respectfully traverse this rejection and submit the Examiner has not set forth a *prima facie* case of obviousness.

The Examiner acknowledged at page 7 of the November 13, 2000 Office Action that "Kolterman *et al.* (II) do not expressly teach that their method is also useful in the treatment of obesity."

In general, Kolterman *et al.* (II) relates to methods of treating patients with type II diabetes mellitus by administration of amylin agonists, in particular ^{25,28,29}pro-h-amylin, which has been the subject of Phase I, II, and III clinical trials over the last several years for uses unrelated to weight reduction. Kolterman *et al.* (II) does not advocate to one of ordinary skill in the art that the presently claimed methods of treating obesity can be accomplished by the administration of an amylin or an amylin agonist. Further, the Examiner has not established that the dosage ranges and routes of administration of amylin agonists in the document cited by the Examiner for treatment of diabetes mellitus are pertinent to the treatment of a different disease, obesity. From this document, it is not clear how one of skill in the art would conclude that any treatment of diabetes, including dosage ranges and routes of administration, would also be

applicable to treatment of the different disease of obesity. Thus one of skill in the art would not automatically apply the teachings of Kolterman *et al.* (II) to methods of treating obesity.

The Examiner has not established a *prima facie* case of obviousness because Meglasson does not provide what is missing from Kolterman *et al.* (II) – the use of an amylin or an amylin agonist for treating or preventing obesity. The Examiner, however, at page 8 of the November 13, 2000 Office Action states:

> A skilled artisan would understand that Kolterman's anti-hyperglycemic compound, ^{25,28,29}pro-h-amylin (i.e., an amylin agonist analogue), would also serve as an anti-obesity agent. Since there is an art-recognized general need for reducing the incidence of human obesity in general and/or diabetic population, one skilled in the art would have been motivated to use Kolterman's method of reducing hyperglycemia in humans to treat obesity for the expected benefit of reducing the increasing incidence obesity, because Meglasson explicitly teaches that any compound useful in the treatment of hyperglycemia could also be used to treat or prevent obesity.

Meglasson's generalization, however, lacks any suggestion that an amylin or an amylin agonist can be used to treat obesity, nor would it have provided motivation necessary to arrive at the claimed invention. Moreover, Meglasson issued as a U.S. Patent on July 28, 1992 from a parent application filed on February 28, 1990, while the present application claims priority as a continuation-in-part to application Serial No. 08/870,762, filed on June 6, 1997. A determination of non-obviousness is made from the reference point of one of ordinary skill in the art at the time the invention was made. Evidence already of record in the prosecution of this application shows that whatever Meglasson's teachings may have indicated to one of skill in the art in 1990 or 1992, by the time the present application was filed amylin and amylin agonists had never before been used or suggested to treat obesity in humans and that studies had actually demonstrated the opposite, namely the effective and preferred use of amylin ***antagonists***, *i.e.*, compounds that actually ***block*** the normal effects of amylin, to treat obesity. Importantly, these teachings in the art were available to one of skill in the art after Meglasson, but before the present priority application was filed in 1997. *See, e.g.*, Amylin Pharmaceuticals' U.S. Patent No. 5,280,014,

issued January 18, 1994 (from an application filed July 18, 1991), and U.S. Patent No. 5,364,841, issued November 15, 1994 (from an application filed June 21, 1993). To this point, the Examiner has failed to fully take into account applicants' evidence of non-obviousness of the claimed invention.

It is the law that any alleged reference "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 U.S.P.Q. 375, 380 (Fed. Cir. 1986). The law further provides that it is clear error to find obviousness where alleged references "diverge from and teach away from the invention at hand." *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Thus, the '841 and '014 patents, discussed above, and the fact that the discoverer of amylin himself taught away from the use of agonists for the treatment of obesity – stating that amylin antagonists should be used instead – is highly probative of nonobviousness.

Also teaching away from the methods of treating obesity described and claimed in the instant application is U.S. Patent No. 5,656,590, issued on August 12, 1997 and claiming priority to a PCT application filed on, and having a 35 U.S.C. § 102(e) date of, May 23, 1992 to Rink *et al.* The Rink '590 patent describes and claims methods for the treatment of patients suffering from anorexia or a similar condition by administering an amylin or an amylin analogue in order to increase weight.

Thus, in contrast to the Examiner's conclusion that it would have been obvious to use an amylin agonist to treat obesity, when taken as a whole in the relevant time frame, the art teaches the opposite, and one of skill in the art would not have been motivated to use the available amylin agonists for methods of treating obesity.

Applicants respectfully request that this rejection also be reconsidered and withdrawn.

Examiner's Response to Applicant's July 24, 2000 Appeal Brief

In the November 13, 2000 Office Action, the Examiner stated that applicants' arguments in their July 24, 2000 Appeal Brief were moot in light of the withdrawal or modification of the

previous art rejections, but then went on to address various statements made in the Appeal Brief. November 13, 2000 Office Action, at ¶ 15.

Applicants respectfully submit that they do not agree with the Examiner's characterization of statements in the July 24, 2000 Appeal Brief, nor with the Examiner's comments at pages 8 through 13 of the November 23, 2000 Office Action. Applicants further submit, however, that no response to the Examiner's comments is necessary because, as stated by the Examiner, the Appeal Brief is moot in light of the Examiner's withdrawal or modification of the rejections addressed by applicants in the Appeal Brief. Applicants reserve the right to respond to the Examiner's statements if the Examiner uses such statements in a rejection against applicants' claims.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance, and seek an early notice thereof. Should the Examiner have any remaining questions, he is encouraged to telephone the undersigned so that they may be promptly resolved.

Respectfully submitted,

Dated: 14 MAY 2001

By: _____
Bradford J. Duft
Reg. No. 32,219

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